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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,091	12/21/2001	Holly Hogrefe	25436/2152	1719

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EXAMINER

HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/035,091

Applicant(s)

HOGREFE ET AL.

Examiner

Richard G. Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 10-14, 20, 22-26 and 30-51 is/are pending in the application.
- 4a) Of the above claim(s) 23-26 and 30-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 10-14, 20, 22 and 36-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants amendment of claims 1, 14, 36, 40, 44 and 50 and cancellation of claims 6, 9, 18 and 21, in the paper of 3/31/2006, is acknowledged. Applicants' arguments filed on 3/31/2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Claims 1-3, 10-14, 20, 22-26, and 30-51 are still at issue and are present for examination

Claims 23-26 and 30-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 10-14, 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 10-14, 20 and 22 remain indefinite in that they are drawn to a mixture comprising a first enzyme that comprises "DNA polymerization activity of a DNA polymerase or reverse transcriptase...". A similar rejection was previously made based on the recitation that the first enzyme comprises a DNA polymerization activity" In response to this rejection applicants amended the recitation to a "DNA polymerization

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activity of a DNA polymerase or reverse transcriptase..." and traverse the rejection.

Applicants submit that applicants have amended the claims such to clarify that the first enzyme has the DNA polymerization activity of a DNA polymerase or a reverse transcriptase.

Applicants amendment and traversal are acknowledged, however, found non persuasive on the basis that applicants amendment does not clarify that the first enzyme has the DNA polymerization activity of a DNA polymerase or a reverse transcriptase, but rather applicants amendment continue to require that the first enzyme has a DNA polymerization activity of a DNA polymerase or a reverse transcriptase and that as previously stated, brings into question what enzymes have "a DNA polymerization activity..." that are not also DNA polymerases or reverse transcriptases. Thus the claims are indefinite or claims 2 and 13 are duplicative of claims 1 and 12.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 10-14, 20, 22, 36-39, 40-43, 44-47 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1, 10-12, 20, 22, 36-39, 40-43, 44-47 and 48-51. In response to the rejection, applicants have amended claims 1, 14, 36, 40, 44 and 50 and cancelled claims 6, 9, 18 and 21 and traverse the rejection as it applies to the newly amended claims. Claims 2, 3, 13 and 14 are included in this rejection for the reasons previously stated for claims 1 and 12.

Applicants note that the claims recite an enzyme that comprises "a DNA polymerization activity" and applicants submit that applicants specification teaches over 30 examples of specific enzymes that fall under this limitation, including 16 different polymerases and 9 different reverse transcriptases and that such is enough to adequately describe the claimed genus.

Applicants argument is acknowledged, however, found non-persuasive on the basis that applicants claims recite as acknowledged by applicants, an enzyme that comprises "a DNA polymerization activity..." and such DNA polymerization activities may encompass activities in addition to "DNA polymerization activity itself", such as DNA binding activity, dNTP binding activity, helicase activity, etc... Applicants have not adequately described those enzymes which comprise the breadth of those activities considered to be encompassed by "a DNA polymerization activity".

Applicants further traverse the rejection on the basis that applicants submit in order to meet the description requirement, applicants need only describe the claimed invention in a manner such that one of skill in the art would understand that at the time of filing, applicants was in possession of the invention as claimed.

Given that applicants claims are drawn to those enzymes comprising any of a number of DNA polymerization activities, applicants have not adequately described the claimed genus.

Applicants specific traversal to the recitation of a JDF-3 DNA polymerase in claims 44 and 50, is acknowledged, however while applicants have adequately limited the claims with respect to SEQ ID NO: 10, the claims remain rejected under this statute for the reasons stated previously with respect to the multiple polymerases that exist in mutant Pfu DNA polymerases.

Similarly applicants amendment of claims 36 and 40, while helping applicants description with respect to the recited polymerases, remain rejected for those reasons stated previously and repeated above .

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 2, 3, 10-14, 20, 22, 36-39, 40-43, 44-47 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme mixture comprising a Pfu DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 19 with a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388, does not reasonably provide enablement for any enzyme mixture comprising a mutant Pfu DNA polymerase comprising one or more mutations at positions Y410, T542, D543, K593, Y595, Y385,

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G387 and G388. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 2, 3, 10-14, 20, 22, 36-39, 40-43, 44-47 and 48-51 are so broad as to encompass any enzyme mixture comprising any mutant Pfu DNA polymerase comprising one or more mutations at positions Y410, T542, D543, K593, Y595, Y385, G387 and G388. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed mutant DNA polymerases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those instantly disclosed mutant Pfu DNA polymerases

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comprising the amino acid sequence of SEQ ID NO: 19, further consisting of a mutation at a position selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any of the specified mutant Pfu DNA polymerases, because the specification does not establish: (A) regions of the protein structure which may be modified and the resulting effect on their activity; (B) the general tolerance of Pfu and other DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any Pfu DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired and the fact that the relationship

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between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polynucleotides of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any enzymic mixture comprising any Pfu DNA polymerase with the specified mutations. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutant polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

Applicants comments in response to the previous statutory type double patenting rejection regarding the canceling of the subject matter of claims 1-3, 6, 9-11, 13-15, 19 and 21-23 of copending application 10/079,241 are acknowledged, however it is further acknowledged that applicants along with the cancellation of claims 1-3, 6, 9-11, 13-15, 19 and 21-23 of copending application 10/079,241, added new claims 64-87 drawn to

overlapping subject matter, thus necessitating a provisional nonstatutory double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 10-14, 20, 22 and 36-51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 64-70, 75-87 of copending Application No. 10/079,241. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed enzyme mixtures of the instant application, comprising a first enzyme and a second enzyme wherein said first enzyme comprises a DNA polymerization activity and said second enzyme is a mutant Pfu DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon are anticipated by and thus obvious over the corresponding claims of copending Application No. 10/079,241, drawn to a enzyme mixture comprising a first enzyme and a second enzyme wherein said first enzyme is an Archaeal DNA

polymerase and said second enzyme is a mutant Archaeal DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant acknowledgment of this provisional rejection is acknowledged, as well as applicants statement of their intent of filing a terminal disclaimer as a means of overcoming the rejection at the time at which the claims are found otherwise allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a stylized flourish extending from the end.

Richard G Hutson, Ph.D.
Primary Examiner
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6/8/2006